

34. A method as in claim 31, wherein the dosage of glutamic acid decarboxylase is 1-500 mg of the glutamic acid decarboxylase per kg patient body weight.
35. A composition comprising glutamic acid decarboxylase in a pharmaceutically acceptable carrier for administration to a human patient.
49. The method of claim 31, wherein the GAD is lower molecular weight GAD (GAD65).
50. The method of claim 31, wherein the GAD is recombinant GAD.
51. The method of claim 31, wherein the GAD is synthesized on a peptide synthesizer.
52. The method of claim 31, wherein the GAD is purified from the central nervous system tissue.
53. The method of claim 31, wherein the patient is a prediabetic patient having autoantibodies to GAD.
54. The composition of claim 35, wherein the GAD is lower molecular weight (GAD65).
55. The composition of claim 35, wherein the GAD is recombinant GAD.
56. The composition of claim 35, wherein the GAD is synthesized on a peptide synthesizer.
57. The composition of claim 35, wherein the GAD is purified from the central nervous system tissue.
58. The method of claim 31, wherein the GAD65 is human GAD65.
59. The composition of claim 54, wherein the GAD65 is human GAD65.

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Please add the following new claims

60. (New) A method for preventing or delaying the development of clinical symptoms of insulin dependent diabetes wherein said method comprises administering to an animal an essentially pure GAD protein or a fragment thereof which, when administered to an animal, prevents or delays the development of clinical symptoms of insulin dependent diabetes.

61. (New) The method, according to claim 60, wherein said GAD protein, or fragment thereof, is a recombinant protein.

Remarks

Applicants note for the record that a telephone interview has been conducted between Richard Schwartz, Examiner Tung, Examiner Chan and the undersigned. The interview considered issues of consistency between the PTO's handling of the present case and that of US 5,762,937 and US 6,001, 360 , assigned to the University of Florida and Tobin, USSN 08/455,725. The Examiner also drew applicants' attention to a reference, not hitherto of record, Petersen et al., *Autoimmunity* 25, 129-138 (1997) (Petersen). The Examiner also raised the issue as to whether the GAD referred to in the present case is the same as that in the other patent filings. The answer to the last issue is yes: the Examiner's attention is drawn to the explanation provided in the response filed Feb 22, 1999 at p. 5, second paragraph.

The new claims are copied from recently issued US 6,001,360. It is noted that similar claims were previously pending in the present case but were cancelled to expedite prosecution in view of a 35 USC 112, first paragraph rejection (see claim 31 as filed).

Although it is believed that the Examiner may no longer adhere to all of the views expressed in the office action in light of the above interview, Applicants will briefly address them using the paragraph numbering of the office action.

10. Applicants maintain that there is no material difference in scope between present claim 31 and claim 1 of the '937 patent above. Any differences in wording between the claims are merely semantic and not material to claim scope. For example, although claim 1 of '937 uses

the term "animal" and present claim 31 uses the term "patient," patients can be animals and vice versa. Further, Applicants maintain that there is no material difference between claim 15 of USSN 08/455,725 and dependent claim 58 in the present case. Both claims are essentially a species of present claim 31 or equivalent claim 1 from the '937 patent (directed to methods employing human GAD65 as the therapeutic reagent). If the Examiner disagrees and believes there are material differences in claim scope, she is asked to state what these difference are and why such differences justify the present application being subject to a 35 USC 112, first paragraph rejection, whereas US 5,762,937 and US 6,001, 360 and USSN 08/455,725 are not.

In the absence of any material differences in scope between the present claims and an issued patent, the PTO does owe the present applicants certain obligations of uniformity and fairness. As noted by Richard Schwartz in the above interview, uniform treatment requires that any decision to issue a rejection that would cast doubt on the validity of an issued patent can only be made at the Group Director level. This procedure has not been followed.

11-18. The Examiner's rejection under 35 USC 112, first paragraph has been subject to much discussion in previous responses and office actions. Applicants maintain their previous remarks, in particular that an unduly high standard of enablement is being applied.

In the interview, the Examiner did not rely on arguments asserted in previous office actions, but instead drew Applicants' attention to a reference hitherto not of record (Petersen). This reference discusses an experiment to test whether GAD is effective in treating BB rats, and reports that the treatment was unsuccessful. This result is in contrast with several previous experiment on NOD mice in which GAD did achieve pharmacological activity. Because rats are a somewhat larger rodent than mice, the Examiner apparently views rats as being more predictive of humans than mice. Thus, the Examiner apparently views this newly cited reference as negating references showing pharmacological activity of GAD in NOD mice.

Applicants respectfully disagree, and maintain that the newly cited reference does not change the overall issues regarding enablement. As indicated at p. 130, col. 1, second paragraph of the Petersen reference, IDDM in humans is thought to have a multifaceted etiology, pathogenesis and genetic predisposition. In most (about 80%) IDDM patients, autoantibodies to GAD appear years before onset of symptomatic disease (see e.g., Petersen et

al., *Diabetes* 44, 1478-1484 (1994) at p. 1480, second column, fourth paragraph (of record)). However, the small residual subset of IDDM patients (about 20%) never develop autoantibodies to GAD. Presumably, this subtype has a different genetic predisposition.

The rationale for using GAD as a therapeutic agent is that GAD is a major autoantigen in the development of IDDM, and administration of GAD initiates tolerization to this autoantigen, thereby preventing further immune damage from occurring. Such a mechanism provides a rationale basis for treatment in the vast majority of IDDM patients who develop autoantibodies to GAD. However, this mechanism would not lead one to expect that GAD would be effective in the small minority of IDDM patients that do not develop autoantibodies to GAD.

The NOD mouse is a good model of the major type of IDDM in which human patients develop autoantibodies to GAD, because NOD mice can also develop autoantibodies to GAD (see Tisch et al., *Nature* 366, 72-75 (1993) at e.g., p. 21, column 1, first paragraph) (of record). The NOD mouse is a genetic strain of mouse that can spontaneously develop autoantibodies to GAD, and subsequently symptoms of IDDM, in a manner similar to development of IDDM in humans. By contrast, the BB rat is not such a close model of the major type of IDDM in humans. The BB rat bears a genotype that results in spontaneous development of symptoms of IDDM. However, unlike the NOD mouse, and unlike most humans, the BB rat never develops autoantibodies to GAD (see Petersen et al. at p. 134, col. 1). Because the BB rat never develops autoantibodies to GAD, there is no reason to expect that therapeutic intervention with GAD would have any effect in the BB rat. However, lack of such an effect in the BB rat, cannot be extrapolated to the major subtype of IDDM in human in which autoantibodies to GAD are present

Because the NOD mouse does develop autoantibodies to GAD, it is a much better predictor of results in the major type of human IDDM than the BB rat. At most, Petersen's results indicate that GAD is not effective in forms of IDDM characterized by absence of autoantibodies to GAD. However, these are only a small percentage of the total population of IDDM patients. The NOD mouse, which does develop autoantibodies to GAD, is a much better predictor of response in the major class of human IDDM patients that also develop autoantibodies to GAD.

For these reasons, it is submitted that as for the other cited references, Petersen does not detract from the expectation that the claimed methods will be of at least some benefit to at least some patients, but at most raises issues concerning the uniformity, degree of efficacy or freedom from side effects. In any event, insofar as Petersen is relied on as indicating that the claimed methods would not be effective in humans, then the same logic applies equally to the '937, '360 patents and the '725 application. In these circumstances, any decision to reject the present claims must be made at the Group Director level to ensure uniformity of treatment between the three families of cases. For the reasons given above, and in previous responses, it is submitted that the rejection should be withdrawn and the present claims indicated allowable subject to interference with the other two families of cases.

19-21. Applicants requests that the rejection over the '937 patent be resolved by interference. A formal request for an interference will be made on indication of otherwise allowable subject matter.

24-25. Claims 35 and 54-57, directed to compositions of GAD and a pharmaceutical carrier suitable for administration to humans remain rejected over Chang & Gottlieb. As previously noted, Chang & Gottlieb discuss a composition of GAD in Complete Freund's adjuvant, an adjuvant that is highly toxic to humans. The Examiner says that it would be obvious to use a pharmaceutical carrier suitable for humans in place of Complete Freund's adjuvant because such carriers are well known. The Examiner also says that a buffer such as PBS would suffice as a pharmaceutical carrier suitable for administration to humans. Applicants respectfully disagree. To take the second point first, ordinary laboratory buffers are not suitable pharmaceutical carriers for administration to humans. Such buffers are not manufactured under GMP conditions required of pharmaceutical carriers, and unless by remarkable coincidence, would not be made up at an appropriate concentration for human administration (usually substantially isotonic). Indeed, many laboratory chemicals are specifically marked as being "reagent grade," "for research use only" or "not for human use" or the like. Moreover, although carriers that are suitable for human administration are certainly well known, one would have no motivation to use one unless human administration were contemplated. The

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teaching that administration of GAD to humans has a therapeutic benefit comes from the present application and not the prior art.

For these reasons, it is submitted that the rejection should be withdrawn. Nevertheless, if the Examiner remains unpersuaded, she is requested to hold this issue in abeyance pending resolution of an interference with the other filings noted above.

27. Claims 58 and 59 stand rejected on the basis that reference to human GAD65 is new matter. The Examiner's attention is directed to e.g., p. 36, lines 27-37 and p. 10, line 2 for support.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,


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